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THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Akira NAKAMURA, et al.

Application No. 10/009,950

Filed: December 14, 2001

For : GOODPASTURE'S SYNDROME
MODEL MOUSE

Confirmation No. 7278

Art Unit : 1632

Examiner: Valarie E. BERTOGLIO

Atty. Docket No. 31671-176197

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PATENT TRADEMARK OFFICE

APPEAL BRIEF

Mail Stop: Appeal Brief - Patents
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Sir:

Appellants submit herewith their Appeal Brief, pursuant to 37 C.F.R. §1.192. Please charge the required fee of \$500 and any additional fees necessary, or credit any refunds, to our deposit account no. 22-0261, referencing our docket no. 31671-176197. A Notice of Appeal was filed on June 23, 2005.

REAL PARTIES IN INTEREST

The real party in interest is Japan Science and Technology Corporation, by virtue of assignment from the Applicants.

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RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants or the Appellants' legal representative, or the assignee, that will directly affect or will be directly affected by or have bearing on the Board's decision in this appeal.

STATUS OF CLAIMS:

Claims 1 and 3 have been finally rejected, and are appealed.

Claims 2 and 4-11 have been cancelled.

STATUS OF AMENDMENTS

No responses have been filed subsequent to the Examiner's final rejection of March 23, 2005.

SUMMARY OF THE INVENTION

Disclosed and claimed is an Fc γ RIIB knockout mouse that has been immunized with type IV collagen and exhibits the diagnostic signs (symptoms) of Goodpasture's syndrome, specifically diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody (claim 1, specification, page 4, lines 5-10).

Fc γ RII is a cell surface receptor that recognizes and binds to the Fc portion of immunoglobulin G (IgG), has a low affinity to monomeric IgG, and binds to polyvalent IgG that has become an immune complex. Fc γ RIIB is a subtype of Fc γ RII that, among its other properties and unlike other FcRs, does not associate with the γ chain. The claimed model mouse of the invention lacks or has an inactivated Fc γ RIIB gene, and has further been immunized with collagen IV. The model mouse exhibits the symptoms of Goodpasture's syndrome, as noted above.

A detailed example of how to make the claimed mouse is described in the specification, e.g., at pages 9-11. At page 9, lines 12-18, the construction of a targeting vector and introduction into ES cells is described. At page 9, line 19 to page 20, line 3, preparation and

isolation of the ES clone, and the steps of preparing the homozygous mice with deficient Fc γ RIIB are described.

Immunization of the Fc γ RIIB deficient mouse to produce the claimed model mouse are described in Example 1. The means for making type IV collagen are described at page 10, lines 5-9. The emulsion formulations for injection are described at page 10, lines 9-16. The procedures for injecting the mice and followup are described at page 10, lines 17-27.

Also disclosed and claimed is a method for screening a remedy for improving the symptoms of Goodpasture's syndrome, specifically diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, by administering test substances to the model mouse and evaluating the effects of the test substances on the mouse (claim 3; specification, page 4, line 17 to page 5, line 11). A decrease in the amount of the symptoms in the model mouse to which the test substance is administered compared to the control indicates that the test substance is effective.

The test mouse to be used in the screening method has been fully described, as summarized above. The means for screening are described, *inter alia*, at page 4, line 17 to page 5, line 11. Briefly, the test substance is administered to the animal after or at the same time it is immunized with type IV collagen, and the severity of the expression of the symptoms of Goodpasture's syndrome is evaluated compared to a control animal.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:

1. Claims 1 and 3 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled.
2. Claim 1 stands rejected under 35 U.S.C. § 103 as being unpatentable over Takei (Nature 379:346-348, 1996) in view of Abbate (Kidney International 54:1550-1561, 1998) or Kalluri (PNAS 91:6201-6205, 1994).

GROUPING OF THE CLAIMS:

Claims 1 and 3 can be considered together for the purposes of the 35 U.S.C. § 112, first paragraph rejection. Claim 3 is not subject to the 35 USC § 103(a) rejection.

ARGUMENT:

1. Claims 1 and 3 are enabled under 35 U.S.C. § 112, first paragraph.

The Examiner has taken the position that the claims are overly broad, and that it would require undue experimentation to practice the invention as claimed. Appellants respectfully submit that there is sufficient information provided in the specification along with the general knowledge available to persons of skill in the art to enable a skilled practitioner to practice the invention as claimed.

Claim 1 recites in detail the features of the claimed model mouse:

- (a) The mouse is a homozygous, nonchimeric mouse whose endogenous genes that code for Fc γ RIIB are inactivated by genetic mutation such as destruction, deficiency, or substitution and whose function of expressing Fc γ RIIB is impaired.
- (b) The mouse is immunized with type IV collagen
- (c) The mouse shows symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody.

The methods for making a mouse having all of these features are described in the specification at pages 9-11. At page 9, lines 12-18, the construction of a targeting vector and introduction into ES cells is described. At page 9, lines 19 to page 20, line 3, preparation and isolation of the ES clone, and the steps of preparing the homozygous mice with deficient Fc γ RIIB are described. Persons of skill in the art can routinely construct other such mice whose Fc γ RIIB is inactivated using these techniques and others known to the skilled artisan. Methods of vector construction and of making such transgenic animals are routine.

Immunization of the Fc γ RIIB deficient mouse and normal control are described in Example 1. The means for making type IV collagen are described at page 10, lines 5-9. The emulsion formulations for injection are described at page 10, lines 9-16. The procedures for injecting the mice and followup are described at page 10, lines 17-27. Other means for obtaining

type IV collagen, formulating emulsions suitable for injection, injecting the mice and obtaining the followup data are known in the art and can be determined by routine experimentation.

Claim 3 recites a method for screening a remedy for improving symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, comprising administering a test substance to a model mouse showing the symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, wherein the model mouse is obtained by immunizing with type IV collagen a homozygous and nonchimeric mouse whose endogenous genes that code for Fc γ RIIB are inactivated by genetic mutation such as destruction, deficiency, or substitution; determining at least one exhibition among diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody; and performing a comparative evaluation with a model mouse used as control to which a test substance is not administered; wherein a decrease in the amount of said symptoms in the model mouse to which the test substance is administered compared to the control indicates that the test substance is effective. In other words, the test substance is to be administered to the model mouse as recited in claim 1, and the symptoms of that mouse are to be compared with those of a similar mouse who has not received the test substance.

The model mouse and means for making it are well described in the specification, as discussed under the arguments in favor of claim 1, above. The means for screening are described in the specification, *inter alia*, at page 4, line 17 to page 5, line 11. Briefly, the test substance is administered to the animal after or at the same time it is immunized with type IV collagen, and the severity of the expression of the symptoms of Goodpasture's syndrome is evaluated compared to a control animal. It is respectfully submitted that the model mouse and the method of screening are both very adequately described in the specification, and that a skilled artisan can follow the guidance of the specification as well as using general knowledge in the art to produce a variety of model animals that can be tested as described.

The Examiner has taken the position that the specification teaches only the disruption of the Fc γ RIIB gene by substitution of the exons S₂ and EC₁ with a neo gene cassette, and that it cannot be predicted what level of activity and what phenotype a mouse resulting from other gene

disruptions would exhibit. Appellants respectfully disagree. The claim recites the symptoms that will be exhibited by the claimed model mouse. It is respectfully submitted that it is a matter of routine experimentation for the skilled artisan, using methods that are known in the art, to make and test mice with other types of disruptions to Fc γ RIIB gene.

Accordingly, it is respectfully submitted that persons of skill in the art will understand how to practice the invention with the scope set forth in claims 1 and 3, and that claims 1 and 3 are enabled. Appellants respectfully request that the rejection of claims 1 and 3 under 35 USC § 112, first paragraph be reversed.

2. Claim 1 is not obvious under 35 U.S.C. § 103 in view of Takai taken together with Abbate or Kalurri.

A. Comparison of the invention of claim 1 and the citations

As noted above, claim 1 is drawn to a model mouse showing symptoms of Goodpasture's syndrome (i.e. diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody). The model mouse is a homozygous and nonchimeric mouse whose endogenous genes that code for Fc γ RIIB are inactivated by genetic mutation such as destruction, deficiency, or substitution and whose function of expressing Fc γ RIIB is impaired, that has been immunized with type IV collagen.

Takai discloses an Fc γ RII deficient mouse that displays elevated immunoglobulin levels in response to thymus-dependent and thymus independent antigens. Takai does not mention collagen IV, nor Goodpasture's Syndrome, nor the constellation of symptoms associated therewith. It is also noted that Takai does not mention the specific form Fc γ RIIB.

Kalluri discloses the induction of symptoms of autoimmune Goodpasture syndrome by immunizing New Zealand white rabbits with the α 3 chain of type IV collagen. Kalluri does not mention Fc γ RII, and does not mention or use Fc γ RII deficient animals.

Abbate discloses the induction of experimental Goodpasture's syndrome by immunizing rats with the α 3 chain of type IV collagen. Abbate does not mention Fc γ RII and does not mention or use Fc γ RII deficient animals.

B. There is no motivation to combine the cited references

Appellants respectfully submit that there would have been no motivation to combine the teachings of Kalluri or Abbate with the teachings of Takai to produce a model mouse exhibiting the symptoms of Goodpasture's syndrome and useful for testing remedies therefore, as disclosed and claimed in the present application, *i.e.* a mouse that is Fc γ RIIB deficient and has been immunized with collagen IV.

First, there is no suggestion in Takai of any relationship of the disclosed model mouse to Goodpasture's syndrome, or to the use of collagen IV, nor can any other nexus be found that would suggest combination of the Takai reference with Kalluri or Abbate.

Second, there is no suggestion in Kalluri or Abbate of Fc γ RII or Fc γ RII deficient animals nor can any other nexus be found that would suggest combination of the Kalluri or Abbate reference with Takai. Kalluri and Abbate used normal experimental rabbits and rats, and there is no suggestion in either reference that would suggest the need to use a Fc γ RII deficient animal.

For this reason, it is respectfully submitted that the combination of Takai with Kalluri or Abbate does not render the invention of claim 1 obvious. Appellants respectfully request that the rejection be reversed.

C. The combination would not have resulted in the invention of claim 1.

Furthermore, even if the cited references Takai, Kalluri and Abbate had been combined (for which Appellants submit there would have been no motivation), it would not have resulted in the present invention, but at best would have resulted in a model mouse that was Fc γ RII deficient and had been immunized with the α 3 chain of type IV collagen. This is not the invention of claim 1.

The logical extension of either Kalluri or Abbate would have been to immunize a wild type mouse with the α 3 chain of type IV collagen. Whether this would have resulted in an experimental mouse with the symptoms of Goodpasture's syndrome is unknown. However, it is known that immunizing wild-type mice with collagen IV does not result in

mice exhibiting Goodpasture's syndrome, as the present inventors have shown in Example 1 of the present specification (see, e.g., page 10, line 27 to page 11, line 9, and Figures 1 and 2). In order to produce the claimed experimental model, the mouse must be FcγRIIB deficient and immunized with collagen IV. This is not suggested by any of the cited references, nor by the combination thereof.

For this reason, it is respectfully submitted that the combination of Takai with Kalluri or Abbate does not render the invention of claim 1 obvious. Appellants respectfully request that the rejection be reversed.

D. Summary of Arguments Against 35 USC § 103 Rejection

In conclusion, it is respectfully submitted that:

- 1) There would have been no motivation for a skilled artisan to combine Takai with Kalluri or Abbate to obtain the present invention as claimed in claim 1; and
- 2) Even if the suggested combinations had been made, it would not have resulted in the invention of claim 1.

For these reasons, reversal of the rejection under 35 USC § 103(a) is respectfully requested.

CONCLUSION

In summary, Appellants respectfully request that the Examiner's rejection of claims 1 and 3 under 35 USC §112, first paragraph, and rejection of claim 1 under 35 USC § 103(a) be reversed and the application be passed to issue.

Respectfully submitted,

Date: 8/22/05

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CLAIMS APPENDIX

Appealed Claims:

1. A model mouse showing symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, wherein the model mouse is obtained by immunizing with type IV collagen a homozygous and nonchimeric mouse whose endogenous genes that code for Fc γ RIIB are inactivated by genetic mutation such as destruction, deficiency, or substitution and whose function of expressing Fc γ RIIB is impaired.
3. A method for screening a remedy for improving symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, comprising the steps of:
 - 1) administering a test substance to a model mouse showing the symptoms of diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody, wherein the model mouse is obtained by immunizing with type IV collagen a homozygous and nonchimeric mouse whose endogenous genes that code for Fc γ RIIB are inactivated by genetic mutation such as destruction, deficiency, or substitution,
 - 2) determining at least one exhibition among diffuse alveolar hemorrhage, glomerulonephritis, and the appearance of antikidney glomerular basement membrane antibody,
 - 3) performing a comparative evaluation with said model mouse used as control to which a test substance is not administered;wherein a decrease in the amount of said symptoms in the model mouse to which the test substance is administered compared to the model mouse to which the test substance is not administered indicates that the test substance is effective.